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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/703,350
Filing Date: October 31, 2000
Appellant(s): MEHRABAN ET AL.

Eric E. DeMaster

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 19, 2008 appealing from the Office
action mailed 2/20/2008

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Mook et al., Biochim Biophys Acta, vol 1705:69-89, 2004, abstract.

Dillman R. O., Annals of Internal Medicine, 111:592-603, 1989.

Weiner L. M. Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999.

Gura et al., Science, v 278, 1997, pp.1041-1042.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 and 69-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention stated as the following:

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting angiogenesis in a tumor comprising administering to the tumor an effective amount of an antibody or antigen

binding fragment thereof that specifically binds and neutralizes a polypeptide comprising SEQ ID NO:76 or binds to an immunogenic fragment of SEQ ID NO:76. Although applicant has amended claims from originally presented *"inhibiting angiogenesis in a mammal comprising administering to the mammal an antibody"* to currently presented *"inhibiting angiogenesis in a tumor comprising administering to the tumor an antibody"*, the Office is examining the claims as originally presented invention as in vivo method of inhibiting angiogenesis in a tumor because original claimed term "administering to the mammal" is drawn to an in vivo method.

The specification teaches that protein of SEQ ID NO: 76 is a secreted glycoprotein referred to as a stanniocalcin precursor (page 25). The specification proposes "neutralizing antibodies to stanniocalcin may be useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment". Thus, the specification appears to broadly claim that the claimed antibodies would predictably provide a therapeutic benefit to humans in need of reducing angiogenesis. For example, the specification teaches that angiogenesis is an important component of a variety of diseases and disorders including tumor growth and metastasis, rheumatoid arthritis, psoriasis, diabetic retinopathy, neovascular glaucoma, etc. (page 12). Thus, the claims broadly encompass methods of treating cancer by administering an antibody that binds to SEQ ID NO: 76. However, the specification lacks critical guidance and objective evidence to predictably enable those of skill in the art to practice the invention with success. For example, there is no evidence that inhibition of stanniocalcin activity or removal of the secreted glycoprotein of SEQ ID NO: 76 results in the inhibition

of angiogenesis with concomitant reduction of tumor cell growth in a mammalian subject. There is no guidance that selective binding of SEQ ID NO: 76 with an antibody would predictably reduce tumor cell growth or metastasis in a mammalian subject. The state of the art currently still considers that reducing tumor cell growth and inhibiting disorders associated with angiogenesis is highly unpredictable. For example, Mook et al., (Biochim Biophys Acta, vol 1705:69-89, 2004, abstract) recently comment on treating cancer by inhibition of angiogenesis by inhibiting the function of the proteins, gelatinases regulation of MMP-2 and MMP-9, involved in angiogenesis stating "*MMP-2 and MMP-9 activity regulates bioavailability and activity of growth factors and cytokines, affects the immune response and is involved in angiogenesis. Because of the multifunctionality of gelatinases, it is unpredictable at what stage of cancer development and in which processes gelatinase activity is involved. Therefore, it is concluded that the use of MMP inhibitors to treat cancer should be considered carefully*". Thus, just with regards to inhibiting angiogenesis in general, there is a high standard of accountability recognized by those in this particular area. Based on the very little guidance in the specification, one of skill in the art would not immediately presume that the antibodies would successfully reduce angiogenesis.

Moreover, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for

treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Again, treatment of cancer in general is at most unpredictable, as underscored by Gura et al., (Science, v 278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of these underscores the criticality of providing workable examples, which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that expression of the stanniocalcin gene is upregulated under endothelial tube-forming conditions and the mRNA is found in cancer tissues, the specification offers no

guidance and or objective evidence that "inhibiting" or neutralizing this activity in a mammal or a tumor would effectively inhibit angiogenesis and treating a tumor.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

(10) Response to Argument

Claims 56 and 69-79 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Claims 56 and 69-79

The following is a summary of claimed invention and related teaching of the specification.

Claims 56 and 69-79 are directed to a method of inhibiting angiogenesis in **any tumor** by **administering** an effective amount of an antibody or the antigen binding fragment thereof that binds and inhibits or neutralizes a polypeptide of SEQ ID NO: 76.

The specification provides the following teachings:

1) the protein of SEQ ID NO: 76 (name: PA23 in this application) is a secreted glycoprotein referred to as stanniocalcin precursor that has been suggested to be involved in calcium and phosphate regulation (page 25).

2) in vitro assay showing that the mRNA of stanniocalcin precursor starts expression at 8 hour-growth of endothelial cell culture and goes down thereafter (page 25 and example 19, figure 23).

3) in situ hybridization showing that the mRNA of the stanniocalcin precursor is expressed in the ductal mammary adenocarcinoma and squamous cell carcinoma (figure 28-29, page 7), and lesser extent in chondrosarcoma and renal cell carcinoma vasculature (page 145-6). No normal controls for in situ hybridization are provided in those figures.

Argument:

Appellant at page 11-12 states:

An enabling disclosure only requires a reasonable correlation to the scope of the claims.
An example is not necessary.
Claim does not lack enablement merely because it encompasses inoperative embodiments.

At page 12-13, Appellant argues:

The specification describes stanniocalcin precursor and provides an accession number for the sequence information.

Applicants have provided in vitro and in vivo evidence that the expression of stanniocalcin precursor correlates with an increase in angiogenesis (example 19).

Applicants also examined tissue samples from tumor tissues and demonstrated expression of stanniocalcin precursor in the tumor vasculature but not in normal vasculature.

In response, the Examiner does not agree that Applicants have provided in vivo evidence that the expression of stanniocalcin precursor correlates with an increase in angiogenesis. Example 19 and the tissue sample examination by in situ described in the specification merely provide an in vitro assay to determine the mRNA of stanniocalcin expression in the cultured endothelial cells and a staining of detecting the mRNA in some, not all of the tumor tissue samples. No normal control sample has been provided. One skilled in the art would not conclude that the stanniocalcin is directly involved or play a role in angiogenesis in tumor based on those results. One skilled in the art would not clearly know why some of the tumor samples (chondrosarcoma and renal cell carcinoma vasculature) have lesser extent staining or lesser expression of the mRNA. If stanniocalcin is involved or plays a role in angiogenesis in tumor, are there angiogenesis in these tumors? Since no objective evidence of using an antibody to the protein SEQ ID NO: 76 in the claimed method and no sufficient teaching on the correlation between the protein of SEQ ID NO: 76 and angiogenesis in the tumors provided in the application one skilled in the art would not be guaranteed to practice the claimed method successfully without undue experimentations.

At page 14, Appellant asserts unpredictability of treatment of cancer does not take into account that a method of inhibiting angiogenesis described in the specification is enabled, antibodies that inhibit angiogenesis in vitro has been shown to inhibit angiogenesis in vivo., the references cited by the Examiner do not accurately reflect the

state of the art of us of antibodies for inhibiting angiogenesis and at least one reference is 20 years old.

These have been considered but are not found to be persuasive for the following reasons:

The claims recite inhibiting angiogenesis in tumor comprising administering tumor an antibody to the protein of SEQ ID NO: 76. The specification teaches that angiogenesis is an important component of diseases comprising tumor growth and metastasis and the present invention provides means to detect, monitor....or treat the occurrence or progression of angiogenesis in these conditions (page 12). Other than the simple statement and teaching on the expressions of the mRNA encoding the protein of SEQ ID NO: 76 in the cultured cell or tumor samples, the specification does not provide any evidence showing administering an antibody to the protein of SEQ ID NO: 76 in any animal model or even in an in vitro angiogenesis model, in which the angiogenesis is inhibited. The expression of the mRNA in the cultured cells and tumor samples does not suggest or teach the protein of SEQ ID NO: 76 playing a role in the angiogenesis in tumor because it is not clear that the expression of the mRNA is the result of an angiogenesis in tumor or results in (initiates) or plays a role an angiogenesis process in tumor. If the expression occurs as a result of an angiogenesis, for example, mRNA detected only in an aged tumor, in which the angiogenesis had been processed, administering an antibody to SEQ ID NO: 76 would not work as claimed.

The references cited by the Examiner include the updated references. For example, the reference by Mook et al., (Biochim Biophys Acta, vol 1705:69-89, 2004)

published recently on inhibition of angiogenesis in tumor by inhibiting the function of the proteins, gelatinases regulating MMP-2 and MMP-9 involved in angiogenesis. Mook et al state *"MMP-2 and MMP-9 activity regulates bioavailability and activity of growth factors and cytokines, affects the immune response, and is involved in angiogenesis. Because of the multifunctionality of gelatinases, it is unpredictable at what stage of cancer development and in which processes gelatinase activity is involved"*. This is also the case for this application. It is not clear at what stage of the cancer the stanniocalcin precursor (SEQ ID NO: 76) as a calcium and phosphate regulator, could function as an angiogenesis factor. Does the stanniocalcin precursor contribute to the initiation of angiogenesis in the cancer development? Or it is merely expressed in the endothelial cells in the tumors that have been formed. It is not clear why the chondrosarcoma and renal cell carcinoma vasculature has lesser extent staining as stated in the specification (page 146). If all of the questions are not answered, one skilled in the art would not consider using an antibody to this protein to inhibit angiogenesis in any tumor because the results are unpredictable.

Regarding the "old" reference used in the rejection, as stated in the rejection since the problems in discovery of new drugs in the current system have not been solved, the references are still valuable and should be taken into account for those skilled in the art in their future works.

At page 14-15, Applicants asserts that the Examiner is requiring Applicants to establish enablement to a higher degree of certainty than is required and that the

standard required for enablement is not one of clinical efficacy because it encompasses inoperative embodiments. The standard for enablement does not require a guarantee or that the method work to inhibit or affect the entirety of the angiogenic process, if any experimentation were required it would be routine experimentation.

These have been considered but are not found to be persuasive for the following reasons:

The claims are directed to a method of inhibiting angiogenesis in tumor comprising administering tumor antibody to SEQ ID NO: 76. The standard for such claimed method would be the skilled artisan to practice the method without a undue quantity of experimentations. The current disclosure does not offer this because showing the expression of stanniocalcin precursor mRNA in cultured endothelial cells or the mRNA in certain, but not all of the tested tumor samples, would not guarantee the method of inhibiting angiogenesis in a tumor with an antibody to encoded protein working. The application provides neither in vitro, nor in vivo treatment with any antibody to the protein of SEQ ID NO:76. Determining whether the treatment method with an antibody to the protein as claimed is not routine experimentation or predictable based on the limited teachings provided in the current specification. Applicant is reminded again that claimed method is not method of screening, is a method of treating.

Regarding the clinical efficacy, the Examiner agrees with Appellant on that the standard required for enablement is not one of clinical efficacy. However, the claimed method, inhibiting angiogenesis in tumor by administering an antibody, does require evidence showing that an antibody to the protein could inhibit angiogenesis in a tumor

condition, which allow one skilled artisan making and/or using the invention or at least showing the correlations between the in vitro and in vivo methods to make the claimed invention predictable and practice without undue experimentation. The current disclosure does not show these because the specification offers no objective evidence, no guidance or direction that inhibiting or neutralizing the activity of stanniocalcin precursor in a mammal or a tumor would effectively inhibit angiogenesis in a tumor.

At page 16, Appellant then states that Applicants have described methods and animal models for determining the efficacy of antibodies, for example, at page 76 of the specification, lines 1-25. Other in vitro and in vivo angiogenesis methods are known to those of skill in the art and the Examiner has not met her burden to show the claimed invention is non-enabled.

These have been considered but are not found to be persuasive for the following reasons:

The following are the teachings on page 76, line 1-25 of the specification:

The efficacy of antibodies specifically binding the PA polypeptides identified herein, and other drug candidates, can be tested also in the treatment of spontaneous animal tumors. A suitable target for such studies is the feline oral squamous cell carcinoma (SCC). Feline oral SCC is a highly invasive, malignant tumor that is the most common oral malignancy of cats, accounting for over 60% of the oral tumors reported in this species. It rarely metastasizes to distant sites, although this low incidence of metastasis may merely be a reflection of the short survival times for cats with this tumor. These tumors are usually not amenable to surgery, primarily because of the anatomy of the feline oral cavity. At present, there is no effective treatment for this tumor. Prior to entry into the study, each cat undergoes complete clinical examination and biopsy, and

is scanned by computed tomography (CT). Cats diagnosed with sublingual oral squamous cell tumors are excluded from the study. The tongue can become paralyzed as a result of such tumor, and even if the treatment kills the tumor, the animals may not be able to feed themselves. Each cat is treated repeatedly, over a longer period of time. Photographs of the tumors will be taken daily during the treatment period, and at each subsequent recheck. After treatment, each cat undergoes another CT scan. CT scans and thoracic radiograms are evaluated every 8 weeks thereafter. The data are evaluated for differences in survival, response, and toxicity as compared to control groups. Positive response may require evidence of tumor regression, preferably with improvement of quality of life and/or increased life span.

In addition, other spontaneous animal tumors, such as fibrosarcoma, adenocarcinoma, lymphoma, chondroma, or leiomyosarcoma of dogs, cats, and baboons can also be tested. Of these, mammary adenocarcinoma in dogs and cats is a preferred model as its appearance and behavior are very similar to those in humans. However, the use of this model is limited by the rare occurrence of this type of tumor in animals.

This section of the specification provides nothing more than contemplation on that antibodies to the generic PA peptides (stanniocalcin is PA23) can be tested in the treatment of spontaneous animal tumors and provides no objective evidence to convince one skilled in the art to use the claimed invention without undue experimentations. As the guidance of MPEP (see below), the Examiner provides reasonable double on whether the invention works as claimed and provides references teaching general problems on the treatment of tumors by antibodies as well as specific problems on inhibiting angiogenesis by an antibody as discussed in the rejection above. "Undue experimentation" has been interpreted as require that the claimed invention be enable so that any person skilled in the art can make and use the invention without undue experimentation. "Test of enabled is whether one reasonably skilled in the art could make or

use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation." (MPEP 2164.01).

Moreover, each angiogenic factor or protein has his own role in angiogenesis, some are critical for the process, some play supporting roles, and some although expressed, may not anticipate or be involved in the process. Neutralization of the activity of one protein does not guarantee to inhibit the entire or part of angiogenesis process. Stanniocalcin precursor although is expressed, neither the instant application, nor the state of the art has provided knowledge what the role of the protein plays in the angiogenesis in tumor and the tumor angiogenic process. As such, one skilled in the art would not be convinced that the claimed invention of administering an antibody to this protein could be used for inhibiting angiogenesis in tumor without undue experimentation.

At page 16-18 Appellant provides post filing references teaching on the gene expression of stanniocalcin in endothelial cells during the angiogenesis and asserts that applicants have provided evidence of the predictability of inhibition angiogenesis using the antibodies (page 19). Each of the references teaches the following points as described by the appellant (page 16-17):

Filvaroff et al., found that transgenic mice over expressing stanniocalcin has significantly higher capillary density in organs and muscles compared with age-matched wild type littermates and the transgenic mice showed a larger increase in vascularity after femoral ligation compared to wild type littermates (page 16, last paragraph).

Gerritsen et al., studied gene expression and found that Stanniocalcin was identified as one of the genes whose expression was upregulated in three in vitro models of angiogenesis (page 17, paragraph 1).

Zlot et al., confirmed that PMA stimulates the release of stanniocalcin from endothelial cells (page 17, paragraph 2).

Kahn et al., demonstrated that stanniocalcin is upregulated in an in vitro endothelial cell tube model. When tube formation was inhibited using a PPAR Ligand, the expression of stanniocalcin was decreased (page 17, paragraph 3).

Those references are reviewed carefully, but not found to support the claimed invention for the following reasons:

First, three (last three) of four references use in vitro models for determining the stanniocalcin gene expression in the endothelial cells during the tube formation, the references provide nothing more than the teaching of the instant specification, this tube formation model gives only a suggestion on that the gene is expressed in the cultured cells during the certain artificial conditions. The model could not provide evidence 1) the corresponding expression occurs in vivo during the neovascularization (blood vessel formation during the tumor development; 2) whether the stanniocalcin protein plays a role in the process of angiogenesis, or it is just induced when the other angiogenesis promoting factor are presented. In another word, the references do not suggest or teach whether inhibiting expressing or neutralizing the activity of this protein could affect the process of angiogenesis, especially the angiogenesis in the tumors. If the stanniocalcin precursor is involved or plays a key role in the process, why has no one in

the references used an antibody to stanniocalcin to reduce or inhibit the angiogenesis? The references merely provide evidence that the gene expression of stanniocalcin could be used as a biomarker for the angiogenesis, not a method of inhibiting angiogenesis in tumor, especially in vivo inhibiting angiogenesis in tumor.

Actually, some of the references teach away from the claimed invention. For example, the reference of Filvaroff et al., shows transgenic mice that express stanniocalcin protein (STC-1) compared to the age-matched wild type littermates (pointed by Appellant) and weight-matched younger mice (not stated by Appellant). Filvaroff et al., describe that the stanniocalcin transgenic mice (STC-1) have relative lower body weight than its wild type littermates (figure 1) and a significantly high baseline vascular density in all tissues relative to that area, which occurs over the next 3-10 days with maximal in-of age-matched control mice (figure 6A). Filvaroff et al., then teach that compared with younger, approximately weight-matched control mice, STC-1 mice exhibited a lower vascular density (less angiogenesis) in all tissues examined (page 3687, column 1). Thus, the in vivo role of stanniocalcin in the angiogenesis has not been established by the state of the art and the instant specification. Could any one practice the claimed invention without further information?

Furthermore, cited reference by Zolt et al., also provides a contradictory teaching to the claimed invention. Zolt et al., teach that stanniocalcin protein (STC1) is an autocrine modulator of endothelial angiogenic response to hepatocyte tumor growth that inhibits endothelial cell migration and reduce the endothelial cord formation on Matrigel (in vivo animal angiogenesis assay, figure 2 and 3). Zolt et al., state that that STC1

may play a selective modulatory role in angiogenesis, possibly serving as a stop signal or stabilizing factor contributing to the maturation of newly formed blood vessels (abstract).

At page 18 Appellant provides more references and asserts that these references show an association of the upregulation of expression of stanniocalcin (STC-1) with tumor tissue undergoing angiogenesis stated as the following:

Gerritsen et al., compared gene expression in colon tumor samples versus normal tissue, and that stanniocalcin was found to be one of the most highly upregulated genes in colon tissue. (page 18, paragraph 1)

McCudden et al., demonstrated that STC-1 and its receptor co-localized in breast cancer cells in 91% of cases (page 18, paragraph 1).

Yeung et al., demonstrated that stanniocalcin was induced in human tumor cells, such as colon carcinoma, nasopharyngeal cancer, and ovarian cancer cultured under hypoxic conditions (page 18, paragraph 1).

Wascher et al., demonstrated that STC-1 mRNA was localized in invasive and ductal carcinoma and STC mRNA was detected in breast cancer cells by in situ hybridization and correlated with primary tumor size, number of positive lymph nodes, and stage of the cancer cell (page 18, paragraph 2).

It is noted that Wascher et al. do not disclose using antibody to detect the STC-1 as stated by Appellant on page 18.

Those references are also reviewed carefully, but not found to support the claimed invention again for the same reason: These references provide nothing more

than the teaching of the instant specification on that the stanniocalcin is detected in some cancer tissues. No antibody treatment has been disclosed in single of these post filing references.

It is also noticed that at bridging page 113-114 of the cited review article, Gerritsen et al., summarize the works on the role of stanniocalcin on angiogenesis as the following:

Several laboratories have reported the up-regulation of STC in angiogenic endothelial cells, either using in vitro assays (e.g., tubulogenesis, treatment with growth factors) or in tumor vasculature in vivo (Bell et al., 2001; Gerritsen et al., 2002; Kahn et al., 2000; Liu et al., 2003; Wary et al., 2003). Zlot:et al. (2003) evaluated several potential roles of STC in endothelial cells. They were unable to demonstrate any effect of rhSTC (recombinant human stanniocalcin) on- endothelial cell proliferating, tube formation, or apoptosis; however, rhSTC was shown to inhibit hepatocyte growth-factor (HGF)-induced endothelial cell migration (discussed above too).

This is another evidence to show if STC protein does not have a role on endothelial cell proliferation and tube formation in angiogenesis, how could its antibody be used to inhibit angiogenesis in tumor?

Appellant on page 18-19 continually argues the reference of Mook cited in the office action that trials were performed on patients with advanced stages of the cancer and the animal experiments showed that MMP inhibitors are effective but only when they are administering in early stage of tumor development. Thus, Mook et al., does not teach that inhibition of angiogenesis is highly unpredictable. Then Appellant gives an

example of antibodies (anti-VEGF) that inhibit angiogenesis in vivo and have been proved by FDA for treating cancer. Appellant further argues that the Examiner has failed to provide any evidence that the model of endothelial tube formation dose not correlate to angiogenesis.

These have been considered but are not found to be persuasive for the following reasons:

First, Appellant seems consider that the angiogenesis in tumor is only involved in the early stage of tumor development, not late stages of the cancer including the metastatic cancer. The term angiogenesis in tumor means "blood vessel formation in tumor tissues". The process is involved in entire process of the tumor formation, tumor growth, and tumor metastasis because blood vessels are required to supply the nutrition for the growing tumor cells and expanding the tumor mass. Second, regarding the approval of anti-VEGF antibodies for treating cancer by FDA, one skilled in the art clearly knows that countless references and in vivo evidence for treating the VEGF expressing tumors with anti-VEGF antibodies have been presented before FDA action. Such evidence for claimed method of using an antibody to stanniocalcin precursor (SEQ ID NO: 76) has NOT been provided in the current application and documented in the art.

Regarding the correlation of angiogenesis with the model of endothelial tube formation, again as discussed above, claimed invention is drawn to a method of inhibiting angiogenesis in tumor by administering an antibody to the protein of stanniocalcin precursor (SEQ ID NO: 76). The endothelial tube formation model

presented in the specification is merely one of in vitro models showing the expression of the protein in the cultured endothelial cells, which could not provide a predication for in vivo inhibition of angiogenesis in tumor by administering antibody to the protein because the role of such expression or the presence of the stanniocalcin precursor in the endothelial cell proliferation and tube formation has not been confirmed as stated above as well as the reference by Gerritsen et al.

Claims 78 and 79

Claims are dependent on claim 56, wherein the tumor is selected from breast, renal squamous, colon and prostrated carcinoma. Since the application does not provide objective evidence to show that the angiogenesis in any of these tumors could be inhibited by an antibody to the stanniocalcin precursor (SEQ ID NO: 76), the claimed invention is not enabled. Appellant argues and presents the same teaching of the example 19 and figure 23 and the reference of McCudden et al, which have been explicitly discussed above.

In summary, given 1) no objective evidence of in vivo inhibition of angiogenesis in tumor with antibody to the protein of SEQ ID NO: 76, 2) unpredictability of in administering an antibody to SEQ ID NO:76 for inhibiting of angiogenesis in tumor based on the expression of the mRNA of stanniocalcin precursor in the cultured endothelial cells and in the tumor samples, and in view of the complex nature of the invention, insufficient disclosure of the instant specificity, and little is know in the art

concerning the claimed invention, it would be undue experimentation for one of skilled in the art to practice the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Lei Yao
/Lei Yao/
Examiner, Art Unit 1642
November 3, 2008

Conferees:

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